REMARKS

The Applicant respectfully disagrees with the Examiner's assessment of the cited documents, and herewith provides the following remarks in response to the claim rejections based on 35 USC § 102 and 35 USC § 103.

Remarks in response to claim rejections under 35 USC § 102

The Applicant is strongly of the opinion that the anticipation rejection of claims 1-6, 8-12, 16, 19, and 22 based on Jansson et al. (US 2008/0044813A1) is reliant on an erroneous interpretation of said disclosure. The Examiner asserts that Jansson et al. teaches detecting pyrophosphate as a ligation by-product to determine whether a ligation reaction has occurred (page 3 of the Office Action), citing p. 1, paragraph 0007, and p. 2, paragraph 0019. However, Jansson et al. is completely unconcerned with pyrophosphate as a means for detection of ligation reactions. Paragraph 0019 merely discloses pyrophosphate as a by-product of luciferase-catalyzed oxidation of luciferin, producing oxyluciferin and light. The present invention teaches, in complete contrast to Jansson et al., the detection of pyrophosphate or pyrophosphate converted into ATP in order to determine the occurrence of a ligation reaction (the pyrophosphate is in fact released from a ligation reaction between at least two oligonucleotides, i.e. a reaction taking place as a result of the catalytic action of a ligase). The production of pyrophosphate in the oxidation of luciferin (i.e. the teaching of paragraph 0019 of Jansson et al.) merely result from ATP-driven oxidation of the biological pigment luciferin catalyzed by the enzyme luciferase, and, more importantly, the pyrophosphate released from said reaction is not in any way utilized for detection. Further, Jansson et al. is also completely silent with regard to converting pyrophosphate into ATP, as per claims 3 and 4 of the present invention, and no paragraph cited by the Examiner is even closely related to said feature. To summarize, paragraph 0019 merely discusses a well-known but completely irrelevant enzymatic reaction, with no significance what so ever for the claimed technical feature of detecting pyrophosphate or pyrophosphate converted into ATP in order to determine whether a ligation reaction has occurred.

Further, the Examiner's citation of paragraph 0007 as a basis for pyrophosphate detection, or detection of pyrophosphate converted into ATP, as a means for ligation reaction determination appears incorrect, as said paragraph is completely silent with regard to pyrophosphate but merely discusses detection of released AMP. In fact, the complete teachings of Jansson et al. are utterly unconcerned with pyrophosphate, or pyrophosphate converted into ATP, as a means for determining the occurrence of ligation reactions, wherefore the Applicant respectfully request that the anticipation rejection based on Jansson et al. is cancelled.

The anticipation rejection of claims 1-6, 9, 14, 16-18, 20-24 based on Schultz et al. (US 6,235,480) analogously rely on a slightly incorrect interpretation of the disclosure in question. The Examiner claims that column 37, lines 22-37 of Schultz et al. teaches converting a ligation by-product into ATP. However, this is a clear misrepresentation of Schultz et al., since said disclosure merely discusses converting products (dNTP or NTP (column 36, lines 55-57), not pyrophosphate) resulting from de-polymerization reactions into ATP for subsequent detection of the de-polymerization reaction per se. Further, the teachings of Schultz et al. regarding pyrophosphate merely relates to pyrophosphate as a reactant in a

pyrophosphorolysis reaction, i.e. an enzymatic de-polymerization reaction involving the cleavage of a terminal internucleoside phosphodiester bond (Schultz et al., column 31, lines 60-67). The pyrophosphorolysis reaction involves a nucleophilic attack on an internucleoside linkage by pyrophosphate, meaning that the pyrophosphate is incorporated into the nucleotide chain (i.e. is not in any way converted into ATP). In fact, in a preferred embodiment taught by Shultz et al., nucleic acid polymerase and pyrophosphate is added to a hybridized sample (Schultz et al., column 36, lines 47-51), i.e. pyrophosphate is not in any way converted into ATP but in fact merely acts as a reactant in the de-polymerization reaction.

The main inventive concept of Schultz et al. concerns identifier nucleotides as analytical output (Summary of the Invention). Column 37, lines 22-37 of Schultz et al., as cited by the Examiner, only discusses the inhibiting effect pyrophosphate is exerting on the luciferase enzyme used for ATP detection, and said passage further goes on to stress the importance of minimizing the amount of pyrophosphate transferred from the pyrophosphorolysis reaction (i.e. the reaction wherein pyrophosphate is acting as a de-polymerizing agent). This paragraph underscores the role pyrophosphate is playing in Schultz et al., i.e. merely as an agent to mediate pyrophosphorolysis of internucleoside bonds, and no paragraph in Schultz et al. has any bearings on the feature claimed in the present invention concerning the detection of the occurrence of a ligation reaction, using either pyrophosphate or pyrophosphate converted into ATP.

The Examiner states that column 22, lines 3-59 of Schultz et al. teaches detecting pyrophosphate as a ligation by-product to determine whether a ligation reaction has occurred, but said passage is in fact completely silent with regards to pyrophosphate. Further, column 41, lines 42-56, also cited by the Examiner as disclosing detection of pyrophosphate, merely discloses the well-known fact that the ATP-driven oxidation of luciferase generates AMP, pyrophosphate, and oxyluciferin, a statement completely irrelevant for the detection of pyrophosphate, or pyrophosphate converted to ATP, to determine whether a ligation reaction has occurred. In analogy with the remarks provided in connection with Jansson et al. above, the production of pyrophosphate in the luceriferase-mediated oxidation of luceriferin cannot be seen as having any significance for the detection feature of present invention, since the present invention discloses the detection of pyrophosphate for determining the occurrence of a ligation reaction, or the conversion of pyrophosphate into ATP for subsequent ligation detection, an aspect completely unrelated to Schultz et al. (and Jansson et al.). Thus, in view of the above, the Applicant respectfully requests that the anticipation rejection based on Schultz et al. is cancelled.

Consequently, the Applicant is strongly of the opinion that the Examiner's 35 USC § 102 rejection of claims 1-6, 8-12, 16, 19, and 22 based on Jansson et al., and claims 1-6, 9, 14, 16-18, 20-24 based on Schultz et al., are reliant on erroneous interpretations of said documents, and respectfully request that the rejections are removed. To summarize, Jansson et al. merely discloses the well-known fact that pyrophosphate is generated in the luciferase-mediated oxidation of luciferin, a fact completely irrelevant for detecting pyrophosphate, or converting pyrophosphate into ATP, to determine whether a ligation reaction has occurred. Further, Jansson et al. merely discusses detection of AMP released from a ligation reaction, meaning that the approach of Jansson et al. is diametrically opposite to the present invention as claimed.

Schultz et al. discloses the same well-known fact concerning luceriferase-mediated oxidation, which again is cited, from the Applicant's standpoint, incorrectly by the Examiner. Further, the remaining teachings of Schultz et al. regarding pyrophosphate merely pertain to the role pyrophosphate is playing in a de-polymerizing pyrophosphorolysis reaction, wherein pyrophosphate is acting as a reactant for the cleavage of internucleoside bonds, again a teaching with no relevance for the present invention as claimed. Neither disclosure teaches using pyrophosphate, or pyrophosphate converted into ATP, as a means for detection of the occurrence of a ligation reaction, and the Applicant consequently respectfully requests that the anticipation rejections shall be removed.

To conclude, since no claim of the present invention can be considered anticipated by the prior art, the Applicant respectfully requests that the 35 USC § 102 rejections are removed.

Remarks in response to claim rejections under 35 USC § 103

Claims 1-6, 8-12, and 14-25 are all non-obvious in view of the cited disclosures, as the person having ordinary skill in the art would not know how to solve the problem of devising a more versatile method for rapid, accurate, quantitative analysis of genetic variation, since neither cited document is concerned with detecting pyrophosphate, or pyrophosphate converted into ATP, for determining the occurrence of a ligation reaction.

Jansson *et al*. is considered to constitute the closest prior art, as it teaches a method for detecting ligase-catalyzed joining of nucleic acid ends, where the detection is based on the release of AMP. The difference between Jansson *et al*. and the present invention as currently claimed is consequently the fact that the present invention employs pyrophosphate for detection (i.e. or pyrophosphate converted into ATP). Utilizing pyrophosphate instead of AMP in the detection implies that the method is more versatile, as different enzymatic reactions relying on different substrates for conversion into ATP can be utilized. The technical problem solved by the invention is thus to provide a more versatile method for determining the presence of a specific genetic element.

Schultz et al. is merely concerned with detection of ATP obtained through conversion of dNTP or NTP using a mixture comprising NDPK enzymes and ADP. However, the conversion of dNTP or NTP into ATP disclosed in Schultz et al. follows a de-polymerization reaction of the oligonucleotides, and not a ligation reaction, meaning that there is a substantially higher risk of obtaining an incorrect read-out, as the de-polymerizing pyrophospholysis reaction is less specific and exact. Additionally, the fact that pyrophosphate is inhibiting the luciferase enzyme is a further complicating factor, resulting in reduced specificity and decreased sensitivity of the detection method per se. Thus, the solution of the present invention as currently claimed, wherein the pyrophosphate is advantageously utilized for the detection or for the conversion into detectable ATP for determination of ligation reactions, implies that the system has been optimized to minimize the risk of obtaining incorrect read-outs and to optimize specificity and sensitivity. There are thus no teachings or motivations in Schultz et al. for the skilled artisan to arrive at the solution to the technical problem, meaning that the present invention as claimed is non-obvious in view of the prior art.

Schalling et al. relies on an entirely different detection principle than the present invention, i.e. ligation of hybridized oligonucleotides and subsequent detection of the ligation products by electrophoresis. Schalling et al. is completely silent with regards to detecting pyrophosphate, or pyrophosphate converted into ATP, to determine whether a ligation reaction has occurred, implying that one of ordinary skill in the art would not find any teachings or suggestions in said disclosure to arrive at the solution presented in the present invention as currently claimed.

The person of ordinary skill in the art would further not find any incentive to combine the cited disclosures to arrive at the invention, as Jansson et al., Schultz et al., and Schalling et al. disclose completely different methodologies with no or very few features in common. Even if the skilled artisan would unexpectedly combine the cited documents, noting in said disclosures would make him arrive at the invention as claimed, wherefore claims 1-6, 8-12, and 14-25 are non-obvious in view of the prior art.

To conclude, there are no teachings or suggestions in the prior art that would motivate the skilled artisan to combine known elements so as to arrive at the claimed invention. Hence, the invention as claimed is not obvious in view of prior art, and the Applicant thus requests that the 35 USC § 103 rejections are removed.

In the event there are any questions concerning this response, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the application may be expedited. In case the Examiner is contemplating issuing a final rejection, the Applicant respectfully requests the Examiner to telephone the undersigned to discuss the matter, in order to expedite prosecution.

No additional fees are believed to be due at this time, beyond the two month time extension fee, however if necessary to effect a timely response the Commissioner is authorised to deduct the necessary fees from Deposit account No. 501249.

Respectfully submitted,

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Date: 7 July 2010